Box 1 Sex considerations in pharmaceutical regulations: some examples

USA

1993: The FDA issued its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs (the "Gender Guideline") that recommended separate analysis of men's and women's responses to drugs.[1] Guidance, not enforceable.
1998: The FDA issued what has come to be known as the "demographic rule," requiring manufacturers of drugs and biological products to present effectiveness as well as safety data by gender, age, and racial subgroups.[1] Has force of law, but does not mention criteria for numbers of women to be included, or require data to be analyzed by sex.
2000: The FDA issued a new regulation allowing the agency to halt research on drugs for life-threatening conditions if men and women having the condition are excluded because of their reproductive potential. No mention of numbers of women and men to be included.
2001: A report by the US Government Accountability Office (GAO) found that ten prescription drugs were withdrawn from the US market since January 1, 1997. Eight of the ten prescription drugs posed higher health risks for women than for men.[2]

2001 – 2013: New research on sex differences in disease pathology and outcomes demonstrate the need for a women-focused approach. Other studies show the under-representation of women in some drug trials and the exclusion of females in preclinical phases. Members of the US Congress and House of Representatives make representations to the FDA.
2014: Beginning in October 2014, the national health research funding agency funds only experiments that use an equal balance of male and female cells or animals — unless a study explicitly and justifiably aims to investigate some sex-specific questions.[3]
2015: The FDA has been producing Drug Trial Snapshots since 2015. A Snapshot shows trial participants by sex, age, race/ethnicity for every newly approved medicinal product.[1] Analyses of effectiveness and toxicity by representative sub-group are not displayed.

2016: The Office of Women's Health launches the Diverse Women in Clinical Trial Initiative. The aim is to raise awareness about the importance of participation of diverse groups of women in clinical research.[1]
2018: A draft guidance to the industry is produced to include pregnant women in clinical trials.[4]

CANADA

1997: The Government of Canada issued the 'Guidance Document on the Inclusion of Women in Clinical Trials,' recommending the inclusion of women of childbearing as well as post-menopausal years in all phases of clinical trials. The sample sizes were to be large enough to enable the evaluation of sex differences in treatment effects.[5] Guidance only. Not enforced.
1997-2013: Studies report better representation of women in third phase clinical trials, but not so in phases 1 and 2, or for pregnant and lactating women; poor representation of females in preclinical phases are also reported.[6]
2009: The Health Portfolio of the Government of Canada updates its sex and gender-based analysis (SGBA) policy. This states that SGBA must be applied to the development, implementation, and evaluation of the Health Portfolio's research, legislation, policies, programs, and services to address the different needs of women and men.
2013: Based on emerging evidence, an updated version of the Guidance Document, 'Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences,' was released, superseding the 1997 document. This version provided advice to researchers on analysis of sex differentials in drug safety and efficacy, and guidance for managing inadvertent pregnancy in trial participants as well as the safe inclusion of pregnant and breastfeeding women.[6,7]
2019: Health Canada establishes a Scientific Advisory Board on Health Products for Women to review practices aimed at preventing further occurrences of market withdrawal of medical products that harm women.[8]

EUROPEAN COMMISSION

2014: The EU Clinical Trial Regulation No 536/2014 required that participants in clinical trials represent the population groups (e.g., age and gender groups) that are likely to use the medicinal product investigated in the clinical trial. Non-inclusion had to be justified. The regulation defined conditions under which pregnant and breastfeeding women could participate in clinical trials. Outcomes had to be analyzed and results presented by age groups and sex.[9,10]

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

2004: Based on the findings from three ICH Regions' surveys, the ICH took the position that the findings did not support the development of a separate ICH Guideline on women. The outcome of the surveys, including the review of existing ICH Guidelines and regional experiences, were reported in an ICH Considerations document and posted on the ICH website. in June 2009, the Considerations document was updated to include the reference to relevant new and revised ICH Guidelines and to reflect the recognized distinction between the concepts sex and gender.[11] The ICH holds that existing requirements in demographic (including gender) characterization, analysis, and assessment of the patient population are adequate to guide clinical trials.[11]

Box 2: Conceptual link of sex and gender, and examples of sex differentiation in intervention dynamics, safety, and efficacy

Sex and gender: Sex refers to the biological attributes of humans and animals, including anatomy, chromosomes, hormones, and gene expression.[12] Gender represents the socially constructed differences between girls/women and boys/men in roles and access to resources and power. Sex and gender interact with each other and with other health determinants.

Biological sex-differences in pharmaceutical response: these are based on genetics, body size and fat distribution, reproductive systems, and concentrations of hormones, enzymes, and other pharmaceutical-target molecules in gut absorption, blood concentration, liver, and kidney clearance rates (pharmacokinetics and pharmacodynamics).[13,14] For example, women have differences in pharmacokinetics linked to increased adverse drug reactions (ADRs) that are potentially caused by insufficient dosage adjustments.[14] Women have a 1.5-2 times higher plasma concentration as men for Zofran, a drug to prevent nausea and vomiting from chemotherapy and used in post-operative patients, which may call for lower dosing among women.[15] Men have higher concentrations of angiotensin-converting enzyme-2 (ACE2)- a therapeutic target for ACE-inhibitors in treating cardiovascular conditions.[16]

Women-specific life course events that influence pharmaceutical response: menstrual cycles, pregnancy, breastfeeding, menopause also can produce physiological and biochemical changes that influence safety and efficacy profiles. Exogenous hormones, in the form of hormonal contraceptives or gender-affirming therapies, cause an increase in estrogen and/or progesterone levels, potentially influencing drug elimination.

Women- differentiated safety and adverse drug reactions: women using rosiglitazone and pioglitazone for type-2 diabetes have a higher risk of fractures. Women using anti-arrhythmia medications such as quinidine are at an increased risk of *torsades de pointes*, a potentially fatal arrhythmia. Women are 1.5-1.7 times more likely to experience an adverse drug reaction (ADR) than men.[17]

Box 1: **Women representation of 50% or less in products registered in 2019 by the FDA [18]**

Active Ingredient	Approved Indication	% Women Participation	Trial Sites and Size
tafamidis meglumine)/ tafamidis	Treatment of the cardiomyopathy caused by transthyretin-mediated amyloidosis (ATTR-CM).	10	1 CT, across 60 international sites; Women: 43/441
Erdafitinib+	For the treatment of urothelial carcinoma (a type of bladder and urinary tract cancer)	21	1 CT across international sites, Women: 18/87
lumateperone	Treatment of schizophrenia in adults.	24	3 CTs, 33 sites across USA; Women:199/818
zanubrutinib	Treatment of adults with mantle cell lymphoma	25	2 CTs, across international sites, Women: 29/118
enfortumab vedotin-ejfv	For the treatment of a type of bladder and urinary tract cancer called urothelial carcinoma.	30	1CT across 40 sites in USA and Japan; Women: 37/125
risankizumab-rzaa	Treatment of moderate to severe plaque psoriasis	30	5 CTs across international sites; Women: 479/1606
Flurodopa F 18	Visual detection of certain nerve cells in adult patients with suspected Parkinsonian syndromes (PS).	32	1 CT across USA; Women: 18/56

polatuzumab vedotin-piiq	Treatment of adults with diffuse large B-cell lymphoma	34	1 CT across international sites; Women: 27/80
fedratinib	Treatment of myelofibrosis	43	1 CT across international sites; Women: 83/192
imipenem, cilastatin, and relebactam	Treatment of complicated urinary tract infection	43	2 CTs, across international sites; Women: 184/430
lefamulin	Treatment of community-acquired bacterial pneumonia (CABP).	44	2 CTs, across international sites; Women: 572/1289
afamelanotide	Increasing pain-free light exposure in adult patients with a history of phototoxic reactions (damage to skin) from erythropoietic protoporphyria	47	3 CT across international sites, Women:115/244
selinexor	Treatment of multiple myeloma	47	1 CT across international sites; Women:94/202
Pretomanid	Treatment of lung tuberculosis in limited population	48	1 CT across 3 sites in South Africa; 52/109
istradefylline	Treatment of “off episodes” in patients with Parkinson’s disease	49	2 CTs across USA, Canada and Japan; Women: 574/1160
cenobamate	Treatment of partial-onset seizures in adult patients.	49	2 CTs across 147 international sites; Women: 323/655
elexacaftor/tezacaftor/ivacaftor; ivacaftor	Treatment of patients 12 years of age and older with the most common gene mutation that causes cystic fibrosis.	50	2 CTs across 154 international sites; Women:253/510
Pitolisant	Treatment of excessive sleepiness due to narcolepsy.	50	2 CTs across Europe and South America; Women: 132/266

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